

Amendments to the Claims:

This listing of claims will replace all prior versions and listings of claims in the application:

Listing of Claims:

Claims 1-10 (canceled)

Claim 11. (currently amended) An isolated human antibody, or an antigen-binding portion thereof, that binds an epitope of human IL-18, or portion thereof, the epitope comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 33, wherein the antibody, or antigen-binding portion thereof, dissociates from the epitope of human IL-18 with a k_{off} rate constant of 0.1 s^{-1} or less, as determined by surface plasmon resonance, or inhibits human IL-18 activity of IFN- γ induction in KG-1 cells (ATCC Accession No. ATCC-CCL-246) with an IC_{50} of $1 \times 10^{-6}\text{ M}$ or less.

Claims 12 and 13. (canceled)

Claim 14. (original) The antibody, or antigen-binding portion thereof, of claim 11, which is a recombinant antibody.

Claim 15. (original) The antibody, or antigen-binding portion thereof, of claim 11, which is a monoclonal antibody.

Claim 16. (canceled)

Claim 17. (currently amended) The isolated antibody of claim ~~16~~11, or an antigen-binding portion thereof, which dissociates from the epitope of human IL-18 with a k_{off} rate constant of $1 \times 10^{-2}\text{ s}^{-1}$ or less, as determined by surface plasmon resonance, or which inhibits human IL-18 activity of IFN- γ induction in ~~KG+~~ KG-1 cells (ATCC Accession No. ATCC-CCL-246) with an IC_{50} of $1 \times 10^{-7}\text{ M}$ or less.

Claim 18. (currently amended) The isolated antibody of claim ~~16~~11, or an antigen-binding portion thereof, which dissociates from the epitope of human IL-18 with a k_{off} rate constant of $1 \times 10^{-3}\text{ s}^{-1}$ or less, as determined by surface plasmon resonance, or which inhibits human IL-18 activity of IFN- γ induction in ~~KG+~~ KG-1 cells (ATCC Accession No. ATCC-CCL-246) with an IC_{50} of $1 \times 10^{-8}\text{ M}$ or less.

Claim 19. (currently amended) The isolated antibody of claim ~~46~~11, or an antigen-binding portion thereof, which dissociates from the epitope of human IL-18 with a k_{off} rate constant of $1 \times 10^{-4} \text{s}^{-1}$ or less, as determined by surface plasmon resonance, or which inhibits human IL-18 activity of IFN- γ induction in ~~KG1~~ KG-1 cells (ATCC Accession No. ATCC-CCL-246) with an IC_{50} of $1 \times 10^{-9} \text{M}$ or less.

Claim 20. (currently amended) The isolated antibody of claim ~~46~~11, or an antigen-binding portion thereof, which dissociates from the epitope of human IL-18 with a k_{off} rate constant of $1 \times 10^{-5} \text{s}^{-1}$ or less, as determined by surface plasmon resonance, or which inhibits human IL-18 activity of IFN- γ induction in ~~KG1~~ KG-1 cells (ATCC Accession No. ATCC-CCL-246) with an IC_{50} of $1 \times 10^{-10} \text{M}$ or less.

Claim 21. (currently amended) The isolated antibody of claim ~~46~~11, or an antigen-binding portion thereof, which dissociates from the epitope of human IL-18 with a k_{off} rate constant of $1 \times 10^{-6} \text{s}^{-1}$ or less, as determined by surface plasmon resonance, or which inhibits human IL-18 activity of IFN- γ induction in ~~KG1~~ KG-1 cells (ATCC Accession No. ATCC-CCL-246) with an IC_{50} of $1 \times 10^{-11} \text{M}$ or less.

Claims 22-25. (canceled)

Claim 26. (currently amended) ~~The~~An isolated antibody, or an antigen-binding portion thereof, ~~of claim 25~~capable of binding human IL-18, wherein said antibody or antigen-binding portion thereof comprises a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 domain selected from the group consisting of:

a heavy chain CDR1 domain of SEQ ID NO: 9 or modified from SEQ ID NO: 9 by at least one amino acid substitution at a position selected from the group consisting of H30, H31, H32, H33, ~~or~~and H35;

a heavy chain CDR2 domain of SEQ ID NO: 10 or modified from SEQ ID NO: 10 by at least one amino acid substitution at a position selected from the group consisting of H52, H52a, H53, H54, H56, ~~or~~and H58; and

a heavy chain CDR3 domain of SEQ ID NO: 11 or modified from SEQ ID NO: 11 by at least one amino acid substitution at a position selected from the group consisting of H95, H96, H97, ~~or~~and H98; wherein the at least one amino acid substitution does not inhibit IL-18 binding to the epitope comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 33.

Claim 27. (canceled)

Claim 28. (currently amended) ~~The~~An isolated antibody, or an antigen-binding portion thereof, ~~of claim 25~~capable of binding human IL-18, wherein said antibody or antigen-binding portion thereof ~~comprises a light chain variable region comprising~~comprising a CDR1, a CDR2, and a CDR3 domain selected from the group consisting of:

a light chain CDR1 domain of SEQ ID NO: 12 or modified from SEQ ID NO: 12 by at least one amino acid substitution at a position selected from the group consisting of L30, L31, L32, ~~or~~ and L34;

a light chain CDR2 domain of SEQ ID NO: 13 or modified from SEQ ID NO: 13 by at least one amino acid substitution at a position selected from the group consisting of L50, L52, L53, ~~or~~ and L55; and

a light chain CDR3 domain of SEQ ID NO: 14 or modified from SEQ ID NO: 14 by at least one amino acid substitution at a position selected from the group consisting of L89, L90, L91, L92, L93, L94, L95, L95a, L95b, L96, ~~or~~ and L97; wherein the at least one amino acid substitution does not inhibit IL-18 binding to the epitope comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 33.

Claim 29. (currently amended) An isolated antibody, or an antigen-binding portion thereof, comprising one heavy chain variable region[[,]] and one light chain variable region, at least one of said variable regions comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 15, 16, and 17, wherein said isolated human antibody, or said antigen-binding portion thereof is capable of binding human IL-18.

Claim 30. (previously presented) An isolated antibody, or an antigen-binding portion thereof, comprising a light chain variable region (LCVR) having an amino acid sequence of SEQ ID NO: 15 and a heavy chain variable region (HCVR) having an amino acid sequence of SEQ ID NO: 16, wherein said isolated human antibody, or said antigen-binding portion thereof is capable of binding human IL-18.

Claim 31. (previously presented) An isolated antibody, or an antigen-binding portion thereof, comprising a light chain variable region (LCVR) having the amino acid sequence of SEQ ID NO: 15 and a heavy chain variable region (HCVR) having the amino acid sequence of SEQ ID NO: 17, wherein said isolated human antibody, or said antigen-binding portion thereof is capable of binding human IL-18.

Claim 32. (canceled)

Claim 33. (currently amended) ~~The~~An isolated antibody, or an antigen-binding portion thereof, ~~of claim 25~~capable of binding human IL-18, wherein said antibody or antigen-binding portion thereof

~~comprises a heavy chain variable region comprises~~comprising a CDR1, a CDR2, and a CDR3 domain selected from the group consisting of:

a heavy chain CDR1 domain of SEQ ID NO: 20 or modified from SEQ ID NO: 20 by at least one amino acid substitution at a position selected from the group consisting of H30, H31, H32, H33, ~~or~~and H35;

a heavy chain CDR2 domain of SEQ ID NO: 21 or modified from SEQ ID NO: 21 by at least one amino acid substitution at a position selected from the group consisting of H50, H51, H52, H52a, H53, H54, H56, ~~or~~and H58; and

a heavy chain CDR3 domain of SEQ ID NO: 22 or modified from SEQ ID NO: 22 by at least one amino acid substitution at a position selected from the group consisting of H95, H96, H97, H98, H99, H100, H100a, H101, ~~or~~and H102; wherein the at least one amino acid substitution does not inhibit IL-18 binding to the epitope comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 33.

Claim 34. (canceled)

Claim 35. (currently amended) ~~The~~An isolated antibody, or an antigen-binding portion thereof, ~~of claim 34~~capable of binding human IL-18, wherein said antibody or antigen-binding portion thereof comprises a light chain variable region ~~comprises~~comprising a CDR1, a CDR2, and a CDR3 domain selected from the group consisting of:

a light chain CDR1 domain of SEQ ID NO: 23 or modified from SEQ ID NO: 23 by at least one amino acid substitution at a position selected from the group consisting of L30, L31, L32, ~~or~~and L34;

a light chain CDR2 domain of SEQ ID NO: 24 or modified from SEQ ID NO: 24 by at least one amino acid substitution at a position selected from the group consisting of L50, L52, L53, ~~or~~and L55; and

a light chain CDR3 domain of SEQ ID NO: 25 or modified from SEQ ID NO: 25 by at least one amino acid substitution at a position selected from the group consisting of L89, L90, L91, L92, L93, L94, L95, L95a, L95b, L96, ~~or~~and L97; wherein the at least one amino acid substitution does not inhibit IL-18 binding to the epitope comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 33.

Claim 36. (currently amended) An isolated antibody, or an antigen-binding portion thereof, comprising one heavy chain variable region[[,]] and one light chain variable region, at least one of said variable regions comprising an amino acid selected from the group consisting of SEQ ID NO: 26, 27, and 29.

Claim 37. (allowed) An isolated antibody, or an antigen-binding portion thereof, comprising a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 29 and a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 26, wherein said isolated human antibody, or said antigen-binding portion thereof is capable of binding human IL-18.

Claim 38. (allowed) An isolated antibody, or an antigen-binding portion thereof, comprising a light chain variable region (LCVR) having the amino acid sequence of SEQ ID NO: 29 and a heavy chain variable region (HCVR) having the amino acid sequence of SEQ ID NO: 27, wherein said isolated human antibody, or said antigen-binding portion thereof is capable of binding human IL-18.

Claims 39-43. (withdrawn)

Claim 44. (currently amended) A pharmaceutical composition comprising the antibody, or antigen-binding portion thereof, of any of claims ~~5-12 and 14-38~~11, 17-21, 26, 28-31, 33, and 35-38, and a pharmaceutically acceptable carrier.

Claim 45. (original) The pharmaceutical composition of claim 44 which further comprises at least one additional therapeutic agent for treating a disorder in which IL-18 activity is detrimental.

Claim 46. (previously presented) The pharmaceutical composition of claim 45, wherein said additional agent is selected from the group consisting of an antibody or fragment thereof capable of binding human IL-12, methotrexate, TNF antagonists, corticosteroids, cyclosporin, rapamycin, FK506, and non-steroidal anti-inflammatory agents.

Claim 47 - 60. (withdrawn)

Claim 61. (canceled)